



REVIEWS

Arrhythmic sudden death in children

Mort subite rythmique chez l'enfant

I. Denjoy^{a,b,c*}, J.M. Lupoglazoff^{a,c}, P Guicheney^c,
A Leenhardt^a

^a Hôpital Lariboisière (AP-HP), Service de cardiologie, Paris.

^b Hôpital Robert-Debré (AP-HP), Service de cardiologie, Paris.

^c Inserm, U582, Institut de myologie, Paris.

KEYWORDS

Sudden death;
Cardiomyopathy;
Channelopathy;
Brugada.

Summary

Sudden death (SD) in childhood is rare, representing only 10% of paediatric mortality after one year of age. The individual risk is estimated between 1 in 20.000 and 1 in 50.000 per year. In case of a negative autopsy for cardiac morphologic anomalies, the most presumable cause remains a genetically-determined malignant primary ventricular arrhythmia. Rhythmic sudden cardiac death can be categorized as a complication of a cardiomyopathy (dilated or hypertrophic), or as a primary channelopathy without any structural heart disease. Primary ventricular arrhythmias include long QT syndrome, Brugada syndrome, short QT syndrome and Polymorphic Ventricular Tachycardia. The diagnosis of such syndromes relies upon specific ECG anomalies, personal history of family members, eventually echocardiography and drug challenge. For some of these diseases, morbid genes have been identified thus rendering possible the management of pre symptomatic or undiagnosed family members within specialized multidisciplinary teams. In case of sudden arrhythmic death in children, the parents and siblings must be examined Rescued sudden death exposes to a high risk of recurrence. In such patients, the automatic implantable defibrillator has dramatically improved survival.

© 2008 Published by Elsevier Masson SAS.

MOTS CLÉS

Mort subite ;
Cardiomyopathie ;
Cannalopathie ;
Brugada.

Résumé

La mort subite (MS) dans l'enfance est rare, représentant seulement 10 % des morts pédiatriques après l'âge de 1 an. Le risque individuel est estimé entre 1/20 000 et 1/50 000 par an. On peut distinguer deux contextes cliniques de MS chez l'enfant : les MS rythmiques sur cœur sain et les MS compliquant les cardiopathies. Lorsque l'autopsie ne retrouve aucune anomalie morphologique permettant d'expliquer la mort subite, la cause la plus vraisemblable reste une arythmie ventriculaire maligne primitivement d'origine génétique. Parmi ces arythmies ventriculaires malignes, dues à des anomalies de fonctionnement primitif des canaux ioniques cardiaques, on distingue le syndrome du QT long, le syndrome de Brugada, le syndrome du QT court et les tachycardies ventriculaires catécholergiques. Le dépistage cardiologique de l'un de ces syndromes repose sur l'analyse de l'ECG, les antécédents personnels de chaque membre de la famille, éventuellement l'échocardiographie ou les tests

* I. Denjoy, Service de cardiologie, Hôpital Lariboisière, 2, rue Ambroise-Paré, 75475 Paris cedex 10.
E-mail: isabelle.denjoy@lrb.aphp.fr

pharmacologiques de sensibilisation. Pour certains de ces syndromes, le ou les gènes en cause sont connus et rendent possible, au sein d'équipes multidisciplinaires spécialisées, la prise en charge des apparentés pré-symptomatiques ou symptomatiques dont le diagnostic n'aurait pas été établi. Toute mort subite rythmique récupérée expose le patient à un risque élevé de récurrence et justifie l'implantation d'un défibrillateur automatique.

© 2008 Published by Elsevier Masson SAS.

Sudden death (SD) in childhood is rare, representing only 10% of paediatric mortality after one year of age. The individual risk is estimated between 1 in 20.000 and 1 in 50.000 per year [1]. It is possible to identify two clinically distinct contexts with underlying heart defects. Congenital heart diseases are either non repairable (fixed pulmonary hypertension in Eisenmenger's Syndrome) or repairable (tetralogy of Fallot or transposition of the great arteries) [2, 3]. Sudden death following repair of other cardiac defects is infrequent (only 0.1/1 000 patients/year). Finally, sudden arrhythmic death can also occur in cardiomyopathy, especially hypertrophic and, more unusually, dilated or restricted cardiomyopathy [4, 5]. In very rare cases, SD can be due to a primary electrical disease in a normal heart. In cases of sudden arrhythmic death in children, the parents and siblings must be examined. The tests depend on the presumed diagnosis of the sudden death.

Sudden death due to primary malignant ventricular arrhythmia (MVA)

The majority of sudden deaths in children, that remain unexplained after autopsy, probably have a primary arrhythmic origin (table 1). Indeed a certain number of ventricular arrhythmias although lethal can be totally undetectable on autopsy. These primary arrhythmias include torsades de pointes degenerating into ventricular fibrillation for congenital long QT syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT), ventricular fibrillation complicating Brugada syndrome or short QT syndrome. The retrospective confirmation of the diagnosis is only possible when the genetic abnormality is identified in the deceased subject or detected in one of the family members.

Congenital long QT syndrome

Congenital long QT syndrome (LQTS) is clinically and genetically heterogeneous. It is characterised by a prolongation of the QT interval, associated with a high risk of life-threatening ventricular arrhythmias (torsades de pointes, ventricular fibrillation) that can lead to syncope and sudden death [6]. The classic distinction between Jervell and Lange-Nielsen Syndrome (the recessive form with deafness) and Romano-Ward Syndrome (the dominant form without deafness) tends to be forgotten in favour of a classification based on recent advances in molecular genetics. The genes responsible for the LQT1, LQT2, LQT5 and LQT6 forms code for potassium channels (*KCNQ1*, *HERG* = *KCNH2*, *KCNE1*, *KCNE2* respectively) while the affected gene in the LQT3 form codes for the cardiac sodium channel (*SCN5A*) (table 1) [6]. The genetic prevalence is currently estimated at 1/5 000 [7]. The LQTS phenotype is characterized by a

prolonged QT interval (QTc > 440 ms) measured in leads D2 or V5. Recently, genetic testing has become one of the reference methods for the diagnosis of LQTS. The genetic and allelic heterogeneity observed in LQTS and the large size of some of these genes makes genetic diagnosis difficult so that it is actually only established in 50-60% of cases (European populations). Analysis of all the ECG tracings from members of the same family increases the specificity and sensitivity for a given patient. Abnormalities in the length and morphology of ventricular repolarisation are part of the diagnostic criteria for LQTS. The triggers for the arrhythmia seem to be dependent on the genotype [8]. Indeed the most frequent trigger of a serious cardiac event in LQT1 is stress, especially exercise. In LQT2 patients, syncope and ventricular arrhythmias are provoked by sound or emotion, while for LQT3 patients cardiac events occur at rest or during sleep [8]. The onset of symptoms is both age and sex dependent. Boys tend to have earlier clinical onset than girls until the age of 15, after which women are more likely to be symptomatic than men [7]. However, it remains very difficult to evaluate the prognosis of this disease in any given patient. The incidence of cardiac events is greater in the LQT1 and LQT2 patients than in LQT3 and the risk increases with the length of the QTc, independently of the genotype. Cardiac mortality is comparable between the three groups but the lethality of cardiac events in group

Tableau 1 Genes responsible for primary ventricular arrhythmias "Channelopathies".

Syndromes	Genes	Effect on current
LQT1	KCNQ1	IKs ↓
LQT2	KCNH2	IKr ↓
LQT3	SCN5A	INa ↑
LQT4	Ankyrin-B	
LQT5	KCNE1	IKs ↓
LQT6	KCNH2	IKr ↓
Jervell syndrome	KCNQ1	IKs ↓
Jervell syndrome	KCNE1	IKs ↓
Timothy syndrome	CACNA1C	Ca++ ↑
Short QT	KCNH2	IKr ↑
Short QT	KCNQ1	IKs ↑
Short QT	KCNJ2	IK1 ↑
Brugada syndrome	SCN5A	INa ↓
CVPT 1	RyR2	Ca++ ↑
CVPT 2	CASQ2	Ca++ ↑
Andersen syndrome	KCNJ2	IK1 ↓

LQT3 is higher. So patients with the LQT1 and LQT2 are more often symptomatic but have fewer lethal events, while those in the LQT3 group are less likely to be symptomatic but with each syncope the risk of death is higher [7]. We have confirmed that in neonatal forms of LQTS with bradycardia due to atrioventricular block (AVB 2:1) the prognosis is poor, especially in the first month of life (figure 1) [9]. Conversely, neonatal LQTS with isolated sinus bradycardia appears to have a better initial outcome. It is possible to identify two groups, one with conduction problems of the type AVB 2:1 which seems to be associated preferentially with mutations in *HERG* and the other with isolated sinus bradycardia associated with mutations in *KCNQ1* [9].

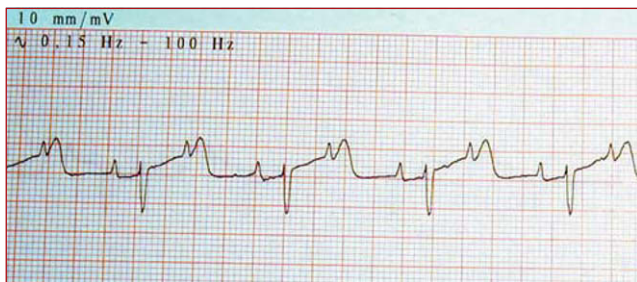


Figure 1. ECG tracing in lead D1 in a newborn. The sinus rate (P-waves) is at 120/mn and the rate ventricular rate (QRS) is at 60/mn due to a functional 2:1 AVB. The QT interval is very long (QTc = 510 ms). One out of two sinus atrial beats occurs during the ventricular refractory period.

Treatment options

Beta-blockers are the standard treatment for the prevention of syncope and sudden death and should be prescribed for all symptomatic patients [6]. Indeed, 20 years ago the rate of sudden death was considerably high, about 70% 10 years after diagnosis, usually occurring within the second or third decades of life. From the years 1975-1980, the use of beta-blockers has lead to a 10 fold decrease in mortality. In our experience, the decrease in recurrences when treated with nadolol, at a dosage of 50 mg/m², is even greater. This remarkable efficacy of beta-blockers in the prevention of SD probably varies according to the genotype. Experimental and clinical data concerning the beneficial effects of beta-blockers have shown that beta-blockers as monotherapy is most appropriate for patients with LQT1, and some patients with LQT2 (often in combination with a permanent pacemaker) but is probably poorly adapted for some LQT3 patients. Therefore, any treatment initiated before the genetic diagnosis is made should be revised once the genotype is known. In all cases of LQTS, whether confirmed or suspected, preventative measures must be established:

- screening and initiation of beta-blocker treatment in all subjects genetically affected whether symptomatic, or not, particularly children;
- prevention of conditions favouring the occurrence of torsades des pointes (hypokalaemia etc.);
- forbid competitive sports and non-competitive sports according to recommendation [10];
- provide children and parents with a list of contra-indicated drugs known to prolong QT interval [6] (www.qtdrugs.org).

Catecholaminergic polymorphic ventricular tachycardia

Catecholaminergic ventricular tachycardia (CVT) is characterised by polymorphic ventricular arrhythmias that are triggered adrenergically. They occur mainly in children and adolescents, and are responsible for syncope and SD in the absence of any other structural heart disease [11, 12]. Cardiac events occur with emotional and/or physical stress, or while swimming. In more than a third of cases, syncope is associated with seizure, thus explaining delays in diagnosis because often the initial treatment is an anti epileptic drug. The baseline resting ECG, shows a normal QTc interval and a mild bradycardia. During stress test, which is the key examination for diagnosis, there is a threshold for the appearance of ventricular arrhythmias which is reproducible and specific for each patient. A characteristic progression is observed with isolated ventricular premature beats, first monomorphic then polymorphic, bigeminy, then bidirectional salvos and finally polymorphic ventricular salvos (figure 2). The genetic basis for CPVT has been elucidated by the finding of autosomal dominant mutations in the gene coding for the ryanodine type 2 receptor (*RyR2*) [12-14]. More recently, two groups have reported closely related forms of CPVT associated with homozygous mutations in the calsequestrin 2 gene (*CASQ2*) which codes for a protein implicated in intra-cellular calcium interactions, and is also situated in the sarcoplasmic reticulum [15]. The *RyR2* and *CASQ2* genes both play a determining role in cardiac excitation-contraction coupling and in the storage and release of intra-cytoplasmic calcium.

In the absence of treatment, the mortality rate in CPVT is very high, reaching 30-50% by the age of 30 years [11, 12]. In addition there is a correlation between the age at which the first syncope occurs and the severity of the disease, the earlier the episodes of fainting first occur, the poorer the prognosis. Beta-blockers have significantly reduced syncope and SD. The doses of beta-blockers used in the prevention of syncope are very high, often twice as those used in LQTS [8]. Nevertheless, it is possible that in adolescents with CPVT incompletely controlled by a high dose of beta-blockers the indication for an implantable cardioverter-defibrillator (ICD) must be more often considered. Patients with CPVT due to mutations in *RyR2* have a varied clinical presentation. Among those genetically affected, 20% show no ventricular arrhythmia during stress test and are



Figure 2. Stress test ECG in a 12 year old child presenting with syncope and seizure during effort.

A. The ECG at rest is normal (QTc = 410 ms). **B.** Appearance of isolated premature ventricular polymorphic beats, first, then couplets when the heart rate reaches 130/mn. **C.** During strenuous exercise, rapid polymorphic salvos occur with near-syncope.

completely asymptomatic. There is a predominance of females (80%) in this healthy carrier group [12]. This observation is in agreement with recent data which show that male gender is a risk factor for cardiac events in patients with *RyR2* mutations [12]. Nevertheless, considering that the first symptom may be sudden death, it is recommended to treat all genetically identified subjects and those patients that are asymptomatic but have ventricular arrhythmia during exercise. Sports is contra-indicated, including for patients treated with beta-blockers.

Brugada syndrome

Brugada syndrome is characterized by a delayed conduction in the right ventricle and an elevated ST segment in the right precordial leads on the resting ECG (figure 3), associated with a high risk of ventricular fibrillation and SD [15-17]. The prevalence of the syndrome is between 4 and 12% of all causes sudden death. The syndrome is responsible for half the sudden deaths occurring in adult patients with apparently normal hearts. The only treatment having any proven effect on the prevention of SD is the implantable cardioverter-defibrillator (ICD). The ECG signs are sometimes intermittent and can be unmasked during a drug challenge with a sodium channel blocker (ajmaline or flecainide in children). Subjects are considered to meet phenotypic criteria if demonstrating typical electrocardiogram anomalies (type 1), either spontaneously on the surface ECG, or during a drug challenge. In case of a symptomatic patient (syncope, aborted sudden death) with typical ECG type 1 Brugada, an ICD is recommended. Ventricular stimulation may be discussed but its diagnostic and prognostic value remains a matter of debate. The symptoms, which in half the cases are syncope leading to death without prodrome, occur primarily in men of 40 years of age. Warning signs are extremely rare in children and occur most often with fever [17]. Probst and co-workers reported the 37-month follow-up of 30 children with Brugada syndrome. In symptomatic children, arrhythmic events occurred mainly with fever with a spontaneous type 1 Brugada ECG. Among the 5 children who received an ICD, 2 had an appropriate shock during follow-up. However, complications are very frequent in implanted children and the indication for ICD in small children remains the exception. Treatment with hydroquinidine could allow to postpone the time to implantation [17]. Asymptomatic children, diagnosed during family screening seem to have a good prognosis [17].

In the context of family screening or systematic discovery, a drug challenge or ventricular stimulation may be proposed for asymptomatic patients over 16 years of age [17]. The genetic origin can be confirmed in approximately 20% of cases, by the identification of mutations in the *SCN5A* gene, which codes for the cardiac sodium channel.

Short QT syndrome

Short QT syndrome (SQTS), is a newly described entity [18, 19] characterized by a short QT interval ($QTc \leq 300ms$) and a high risk of syncope and SD due to malignant ventricular arrhythmias. The phenotype of three families has been recently published. The syndrome is hereditary, since in the affected families, the phenotype is found in several patients from different generations. The syncope and SD may occur at rest but also during effort. The electrocardio-

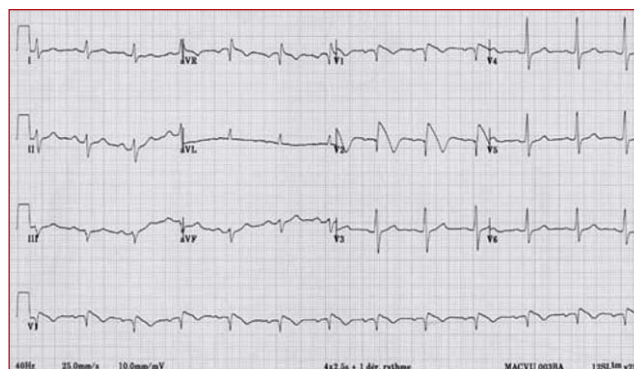


Figure 3. 12 lead ECG recorded in a 12 year-old child after a syncope, showing a type 1 Brugada ECG pattern in leads V1 and V2.

graphic anomaly (QTc) is sometimes associated with early onset of atrial fibrillation. Mutations in the genes *HERG* ($=KCNH2$), *KCNQ1* and *KCNJ2* have been identified in patients with SQTS [19]. Expression studies of these mutations show a shortening of the action potential. Electrophysiological studies show decreased atrial and ventricular refractory periods and ventricular vulnerability to arrhythmia in the majority of patients. ICD implantation is the only treatment available which has proven efficacy in sudden death prevention.

Support for families in the event of sudden death in one of the children

Cardiological screening for one of these syndromes is based on the analysis of the ECG, medical history of each family member, and eventually echocardiography or drug challenge. For most of these syndromes, the morbid gene (or genes) are known and allow, in conjunction with clinical examination, the screening of family relatives, both symptomatic and asymptomatic. This type of screening can not be considered as a routine examination. The indications must be carefully examined and the families should be referred to multidisciplinary teams, which include a cardiologist, a geneticist and a psychologist. The patient must be fully informed of the implications of the test. Time for decision must be respected. Results must be given as part of a programme which includes long-term follow-up.

Presymptomatic diagnosis

Presymptomatic testing of the relatives of an affected patient can enable the identification of those who are at risk of cardiac events and could benefit from close cardiological monitoring. However, given the absence of a curative treatment, and sometimes preventive treatment, the test must be carried out only after the patient has been fully informed during a multi-disciplinary consultation. Indeed, ICD is the only therapeutic option that has proven benefit in the secondary prevention of SD.

Prenatal counselling

When there is a known familial mutation, the diagnosis is technically possible from the 10th week of pregnancy, although

not without risk for the foetus. The test should perhaps therefore only be considered if the decision for abortion depends on the outcome. For an affected parent the risk of transmitting these autosomal dominant syndromes is 50% and it is impossible to predict the penetrance of the disease. Therefore, prenatal diagnosis is not performed for LQTS and catecholaminergic polymorphic ventricular tachycardia because preventive medical treatment exists for these syndromes.

The diagnostic test

Molecular biology allows to confirm the gene involved and the type of mutation. When the mutation has been identified in the proband, it can be easily identified in presymptomatic relatives.

Prognostic evaluations

The identification of patients at high risk of arrhythmic complications can lead to prophylactic measures. For LQTS, the genotype is one of the parameters for risk stratification.

Conclusion

The majority of children who experience SD have known heart diseases, particularly repaired congenital heart defects. Sometimes no morphological abnormality are found at clinical examination or autopsy to explain the SD. In these children, the most likely cause remains a primary malignant ventricular arrhythmia due to a morbid gene. In case of a negative autopsy, it is recommended to biopsy cardiac tissue. Subsequent DNA analysis can provide data supporting a hereditary arrhythmic syndrome. Family members should be sent to centres used to deal with such conditions who work in multidisciplinary teams with the support of a cardiologist, a geneticist, a psychologist and a molecular biologist.

References

- [1] Wren C. Sudden death in children and adolescents. *Heart* 2002; 88:426-31.
- [2] Silka MJ. A population-based prospective evaluation of risk of sudden cardiac death after operation for common congenital heart defects. *J Am Coll Cardiol* 1998;32:245-51.
- [3] Gatzoulis MA. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot : a multicentre study. *Lancet* 2000;256:975-81.
- [4] Watkins H. Sudden death in hypertrophic cardiomyopathy. *N Engl J Med* 2000;342:422-4.
- [5] Muller G, Ulmer H, Hagel K, Wolf D. Cardiac dysarrhythmias in children with idiopathic dilated or hypertrophic cardiomyopathy. *Pediatr Cardiol* 1995;16:56-60.
- [6] Lupoglazoff JM, Denjoy I, Guicheney P. Apports de la génétique dans la prise en charge du syndrome du QT long congénital. *Arch Mal Coeur* 2003;96:539-47.
- [7] Zareba W, Moss AJ, Schwartz PJ, et al. Influence of the genotype on the clinical course of the long-QT syndrome. *N Eng J Med* 1998;339 :960-5.
- [8] Schwartz PJ, Priori SG, Spazzolini C, et al. Genotype phenotype correlation in the long QT syndrome: specific triggers for life-threatening arrhythmias. *Circulation* 2001;103:89-95.
- [9] Lupoglazoff JM, Denjoy I, Villain E, et al. Long QT syndrome in neonates. *J Am Coll Cardiol* 2004;43:826-30.
- [10] Maron BJ, Chaitman BR, Ackerman MJ, et al. Recommendations for physical activity and recreational sports participation for young patients with genetic cardiovascular diseases. *Circulation* 2004;109:2807-16.
- [11] Leenhardt A, Lucet V, Denjoy I, Grau F, Ngoc DD, Coumel P. Catecholaminergic polymorphic ventricular tachycardia in children. A 7-year follow-up of 21 patients. *Circulation* 1995; 91:1512-9.
- [12] Denjoy I, Postma A, Lupoglazoff JM, et al. Tachycardies ventriculaires catécholergiques chez l'enfant. *Arch Mal Coeur* 2005;98:506-12.
- [13] Laitinen PJ, Brown KN, Piippo K, et al. Mutations of Cardiac Ryanodine Receptor (RyR2) gene in familial polymorphic ventricular tachycardia. *Circulation* 2001;103:485-90.
- [14] Postma A, Denjoy I, Hoorntje TM, et al. Absence of calsequestrin 2 causes severe forms of catecholaminergic polymorphic ventricular tachycardia. *Circ Res* 2002;91:e21-e26.
- [15] Brugada J, Brugada R, Brugada P. Right bundle-branch block and ST segment elevation in leads V1 through V3. A marker for sudden death in patients without demonstrable structural heart disease. *Circulation* 1998;97:457-0.
- [16] Wilde A, Antzelevitch C, Borggrefe M, et al. Proposed diagnostic criteria for Brugada syndrome : consensus report. *Circulation* 2002 ; 106 :2514-19.
- [17] Probst V, Denjoy I, Meregalli P, et al. Clinical aspects and prognosis of Brugada syndrome in children. *Circulation* 2007 115: 2042-48.
- [18] Brugada R, Hong K, Dumaine R, et al. Sudden death associated with short QT syndrome linked to mutations in HERG. *Circulation* 2004;109:30-5.
- [19] Lupoglazoff JM, Denjoy I. Syndrome du QT court familial. *Rev Prat* 2007;57:121-5.